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Montgomery, Alabama

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In Vivo Kinetic Behavior of ^{85}Kr in the Whole Guinea Pig

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Introduction

Krypton-85 is widely recognized as a potentially troublesome environmental contaminant produced by the nuclear industry and is becoming widely used in medicine and industry for diagnostic procedures and non-destructive testing. The present $(MPC)_a$ for ^{85}Kr is based on calculations of dose received in an infinite hemispheric cloud, as set forth for noble gases in ICRP-II[1] which involve several assumptions which have not been experimentally confirmed. One such assumption is that the dose from the gas contained in the body tissues is insignificant in comparison to the dose received from the gas outside the body. This assumption appears valid for gamma emitting noble gases but the situation is not so clear when an alpha emitter or a beta emitter, such as ^{85}Kr is involved and the external dose is to superficial tissues rather than the whole body or when modifying factors such as protective clothing or lack of an infinite cloud are considered. Assessment of the total hazard associated with ^{85}Kr exposure must, therefore, include evaluation of the dose from gas in the body tissues which, in turn, requires detailed knowledge of its *in vivo* kinetic behavior.

Background

Study of kinetic behavior is, in essence, evaluation of the capacity of a tissue or aggregate of tissues to hold ^{85}Kr and the rate(s) at which it (they) will reach that capacity during an exposure or, alternately, give up the krypton when the exposure ceases. A common measure of the capacity of the tissue for ^{85}Kr is the partition coefficient (λ) which, for our purposes, is the ratio of the equilibrium concentration (volumetric) of ^{85}Kr in the tissue to the concentration in the air being breathed and is usually written λ tissue:air (slide 1). The λ tissue:air is the product of

λ tissue:blood and λ blood:air. For a complex syste

λ tissue:air = Σ (λ_i tissue:blood x f_i) blood:air (slide 2)

where: λ_i = tissue; blood partition coefficient for component i

f_i = fraction of tissue made up of component i

The rate of absorption of ^{85}Kr into the tissues of the body during exposure and desorption after exposure or injection of the isotope is a complex function of the tissue:blood partition coefficients and, particularly, the blood circulation in the tissue in question. The curves obtained will have as many exponential components as there are differently perfused elements in the tissue being studied. Kety[2] has discussed the kinetics involved in detail. For a single tissue, with the concentration in alveolar air considered constant and blood-tissue diffusion time considered negligible (actually less than 1 sec.), the following equations apply:

Saturation: $C_i = \lambda_i C'_a (1 - e^{-kt})$

Desaturation: $C_i = C_{i(o)} e^{-kt}$

where: C_i = concentration in tissue i at time t, $\mu Ci/cm^3$

λ_i = tissue:air partition coefficient

C'_a = concentration in air, $\mu Ci/cm^3$

k = F_i/V_i where F_i = blood flow rate in tissue i, and V_i = volume of tissue i

The quantity of gas in the tissue (Q_i) = $V_i C_i$ or $Q_i = V_i \lambda_i C'_a (1 - e^{-kt})$ in saturation (slide 3). $Q_{i(\infty)} = V_i \lambda_i C'_a$. For the whole body, or a multiple compartment tissue, $Q = Q_{1(\infty)} (1 - e^{-k_1 t}) + Q_{2(\infty)} (1 - e^{-k_2 t}) + \ldots$ $Q_{n(\infty)} (1 - e^{-k_n t})$ in (slide 4) saturation. Corresponding equations can be written for desaturation.

<u>In vivo</u> behavior of ^{85}Kr, including partition coefficients and rate constants, has been described by a number of authors (3 - 28) who have used

it as a tool for studying regional blood flow and, in 1 case, body fat content. Their data are summarized in tables 1 and 2 (slides 5 and 6). With 2 exceptions, the studies involved rapid injection of Kr into the arterial blood supply to the tissue or direct injection into the tissue followed by study of the clearance curves. These data do not represent a fully saturated condition and the values may not, therefore, be applicable. Tobias et al[27] had human volunteers breathe a constant concentration of ^{81}Kr or ^{79}Kr from a closed spirometer circuit for up to 300 minutes while observing count rates in a knee and a hand (closely shielded/collimated GM detectors) and then followed the count rates for 10-12 hours while the subjects breathed room air. Hytten, in a whole-body fat content study reported complete saturation in 90-180 minutes in human subjects breathing ^{85}Kr from a closed spirometer circuit; but also reports an 18 hour biological $T_{\frac{1}{2}}$ in the desaturation phase. (The complete saturation appears to be an exper mental artifact). Most investigators report a 2-4 component multiple exponential curve. The observations indicate that there are about 4 groups of similarly perfused tissues that may act as compartments for purposes of predicting whole body behavior. The $T_{\frac{1}{2}}$'s are approximately 0.04-0.8 min., 1-5 min., 5-10 min., and 11-180 min. It is especially noted, however, that anything that changes the absolute or relative blood flow will radically affect the observed $T_{\frac{1}{2}}$'s and even change the number and composition of compartments observed.

Lesser and Zak[23] proposed a parallel kinetic model for fat soluble gas uptake consisting of the blood in equilibrium with three compartments: 1. Rapidly perfused lean tissues such as the heart, brain and kidneys; 2. More slowly perfused lean tissue (resting muscle, skin, connective tissue, etc.); and 3. Adipose tissue. The literature data appears to support such an analysis, and it has been used as the basis for the hypothetical saturation and desaturation curves for standard man shown in figure 1 (slide 7). Data

presented later in this paper indicate, however, that the *in vivo* $T_{\frac{1}{2}}$'s in fully saturated animals are considerably longer than most of those in the literature, and saturation and desaturation will be slower than depicted.

Methods and Materials

The whole body kinetic behavior of ^{85}Kr in the whole guinea pig was investigated by counting the 0.514 MeV gamma radiation from guinea pigs breathing an ^{85}Kr-air mixture of known concentration. The exposures were carried out using 1 chamber of a special 10 animal life support and exposure system which will be fully described in a later paper (Figure 2 - slide 8). The animal is placed in a lucite body chamber with its head protuding through a rubber gasket (neck shaved, silicon grease seal). The body chamber is attached to the main system with the animal's head in the circulating Kr-air mixture while the rubber gasket prevents the Kr from entering the body chamber. A scavenging air flow through the body chamber ensures that any leaking Kr is carried away. The circulating system provides respiratory gas control (O_2 about 21%, CO_2 0.2%, and Kr containment. A collimated 4" x 4" NaI (Tl) crystal, coupled to 1 channel of a 2-channel analyzer, is placed directly beneath the animal and extensive shielding added to reduce background and minimize extraneous count from the ^{85}Kr in the circulating system. The ^{85}Kr concentration in the circulating mixture is continuously monitored by an end window GM detector coupled to the other scaler of the 2-channel analyzer. The gas concentrations used to calculate partition coefficients were determined by counting gas samples versus an NBS ^{85}Kr standard in a well counter (NaI). The readings on the GM system were correlated to simultaneous readings on the NaI system, after correcting for different resolving times, for several concentrations of Kr in the circulating mix (water phantom in the body chamber and neck opening) and the values obtained used to adjust experimental data so that the data points reflected only ^{85}Kr in the animal.

The counting efficiency of the NaI system was determined using an NBS ^{85}Kr standard in a water phantom and confirmed using different volumes of ^{85}Sr solution in the same geometry. The efficiency was essentially constant with phantoms larger than 500 ml and the average value of 56.16 CPM/μCi for volumes 500-1200 ml is used in the partition coefficient studies.

A complete experiment consisted of: 1. placing the animal in the system; 2. taking a 20-30 minute background count while the animal breathed room air; 3. exposing the animal to ^{85}Kr while taking frequent simultaneous GM and NaI counts until the NaI count appears to remain constant for about 30 minutes; and 4. then shifting the animal to room air while continuing counting until the count essentially reached preexposure background.

The counting data obtained were processed with an electronic calculator programed to make the necessary resolving time corrections, conversion to NCPM, interference corrections and calculate the composite standard deviation (including standard deviation of counter and animal background, determination of interference, and the count) and print out the midtime of the count, and animal NCPM ± 2 standard deviation for plotting. These points for the desaturation phase were plotted on semilogarithmic paper and resolved into the least number of exponential components that would adequately describe the data using least squares exponential fitting programs and curve stripping programs on an electronic calculator. The correlation coefficients of the curves thus determined were all in excess of 0.999. For intercomparison, all curves were normalized to their own extrapolated equilibrium CPM.

An example of a normalized smooth desaturation curve, plotted versus the data from which it was derived, is shown in figure 3 (slide 9).

Saturation data were not separately resolved because of the large standard deviations in the data near the end of the saturation phase

(resulting from high count rates). The saturation data for each animal was plotted versus the smooth curve generated from the parameters calculated from the desaturation data. On the average, the animals saturated slightly less rapidly than they desaturated. In several cases, however, the curves matched almost perfectly and in one case, saturation was more rapid. The correlation coefficients for fit of the these data ranged from 0.865 to 0.996. A normalized linear plot of an entire run is shown in figure 4 (slide 10). The normalized smoothed desaturation curves for 8 animals are shown in figure 5 (slide 11) along with a plot of an average curve generated by averaging the values of the smooth curves at various times. Variations are marked. No statistically significant differences were found between sexes although 3 or 4 females desaturated more slowly than 3 of 4 males.

The data from the desaturation curves are summarized in table 3 (slide 1). Six or eight animals had 4 compartment curves.

Whole body partition coefficients on a weight rather than volume basis were determined by calculating the specific activity of Kr in the animal at saturation (μCi/g), and dividing by the exposure concentration.[1] These data are shown in table 4 (slide 13). No statistically significant differences could be shown between sexes for these data.

In view of the Lesser and Zak model mentioned earlier, the fraction of the total CPM attributable to fat was estimated and compared to the fraction of the total activity attributable to the longest $T_{\frac{1}{2}}$ component of the desaturation curves and to the sum of the components having $T_{\frac{1}{2}}$ greater than 20 minutes. The fat CPM was greatly in excess of the fraction associated with

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(Note[1]: Difference between partition coefficient calculated on a weight basis and the value on a volume basis is no more than 2% in the animals studied).

the longest component and about 10% higher than the fraction of activity in components with $T_{\frac{1}{2}}$ longer than 20 minutes. The fat fraction estimation is dependent, however, on the partition coefficients used, and considerable variation exists in reported values.

Figure 6 compares the average curve determined for guinea pigs in these investigations and a curve that is an average desaturation curve of 3-250 female Rochester Wistar rats taken in a preliminary study. The rats appear to desaturate faster than guinea pigs but the variations are such that the differences are of marginal statistical significance. The rats were studied by unrestrained saturation in a chamber followed by intermittant restraint in a plastic cylinder while being counted in a 3 x 5 well in a 5 x 7" NaI crystal. The different conditions may have affected the results.

Conclusions

The whole body partition coefficients vary with fat content of the animal but are not correlated in any simple way to weight. The rates of saturation and desaturation vary widely from animal to animal, as do the shape of the saturation and desaturation curves. In the unanesthetized animal it is doubtful if close agreement in these curves can be obtained, even in the same animal, and very large numbers of animals will be required to demonstrate any differences in sex for the parameters studied.

The data reported here together with the observations of Tobias et al[27] and Hytten[28] indicate that time required for saturation and desaturation may be directly correlated to weight of the animal.

Table 1

^{85}Kr Partition Coefficients

Tissue	Part	Tissue:Blood	Tissue:Air
Brain	Cortex	0.92 (Hc=50)	
	White	1.26 (Hc=50)	
Kidney	Cortex	1.0	
		0.96	
	Medulla	1.0	
Fat		9	
			0.54
		5	
Liver		1.06	
		1.04	
Eye	Retina	1.0	
Skeletal muscle		1.0	
Testis		0.85	
Blood			0.05-0.06

Table 2

COMPARTMENTAL ANALYSIS AND $T_{\frac{1}{2}}$'s KRYPTON FROM LITERATURE

Tissue	No. of Compart.	$T_{\frac{1}{2}}$'s (min)	Species	Kr Given by
Brain	2-4	0.1-0.2; 0.2-1.6; 1.6-9; 23.5	rabbit, cat, dog, man	IA injection Direct tissue injection
Heart	1-2	0.34-1.5; ~ 7	dog, man	IA injection (coronary artery)
Kidney (cortex)	1*	0.15-1.17	dog	IA injection
Liver	1-4	0.004-0.32; 0.8; 2.5; 25	dog	IA, IV injection (hepatic artery portal vein)
Stomach	3	0.5-1.15; 3.5-7; NR	cat	IA injection
Intestine	4	0.8; 1.32; 5.45; 41.3	cat	IA injection
Eye	4*	0.05-0.083; 0.25-.28; 1.5-3; 9-44	cat	IA injection
Testis	1	7.1 (probably has shorter component)	ram	IA injection
Leg	1*	11-27	dog	IA injection
Muscle (arm)	1**	8.5-35	man	IM injection
Muscle (scalp, neck)	1	14-20	dog	IM injection
Hand	3	2-10; 10-50; 100-320	man	inhalation-300 min.
Knee	3	NR; 35-72; 190-870	man	inhalation-300 min.
Whole body	NR	T_B1/2 18 hrs. desat. ***	man	inhalation 90-180 min.

* GM counter, superficial tissue only.
** Assumed monoexponential clearance. Data doesn't seem to confirm.
*** Also claims full saturation in 90-180 min.

NR Not reported.

Table 4

Guinea Pig Whole Body Partition Coefficient Data

Parameter	Males (4)		Females (4)		All (8)	
	Av.	S. D.	Av.	S. D.	Av.	S. D.
λ^1 (C_T/C_A)	0.1200	0.0046	0.1376	0.013	0.1288	0.0132
Fat Fraction (g fat/g animal)	.0.1111	0.0086	0.1437	0.025	0.1274	0.0244
Fat CPM/tot. CPM	0.555	0.021	0.623	0.048	0.589	0.05
$\frac{\text{CPM } T_{\frac{1}{2}} > 20 \text{ min.}}{\text{Total CPM}}$	0.635	0.13	0.662	0.16	0.649	0.14
$\frac{\text{CPM longest compart.}}{\text{Total CPM}}$	0.0661	0.06	0.076	0.07	0.071	0.06

C_T = Average μCi ^{85}Kr/gram tissue

C_A = μCi ^{85}Kr/cm^3 air

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GUINEA PIG WHOLE BODY PARTITION COEFFICIENTS (λ)

	MALES (4)		FEMALES (4)		ALL (8)	
	$\bar{X}$	σ	$\bar{X}$	σ	$\bar{X}$	σ
*λ	.120**	.005	.138**	.013	.129	.013

* TISSUE DENSITY ASSUMED TO BE 1.0. MAXIMUM ERROR IN λ 2%.

** DIFFERENCE NOT STATISTICALLY SIGNIFICANT.

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** DIFFERENCE NOT STATISTICALLY SIGNIFICANT.

DESATURATION ANALYSIS -- 8 GUINEA PIGS

COMPONENT	k_c/k_a	$T_{1/2}$ (MIN.)	NO. ANIMALS
1	.09 - .21	2.5 - 4.4	
2	.089 - .49	6.0 - 31.8	1
3	.41 - .61	21.5 - 41.7	8
4	.009 - .17	66.0 - 138.0	7

ACTIVITY COEFF.	10%	50%	90%	95%
TIME (MIN.)	3.87	18.3	97.1	352
σ	.27	3.47	17.1	23.9

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Desaturation Analysis - 8 Guinea Pigs

Component	A_i/A_T	$T_{1/2}$ (min)	No. Animals
1	.019 - .23	1.3 - 2.2	7
2	.069 - .45	6.0 - 21.8	8
3	.41 - .63	22.5 - 121	8
4	.009 - .37	88.0 - 176.0	7

Activity Lost	10%	50%	90%	95%
Time (min.)	0.77	18.2	97.4	152
σ	.27	3.83	10.1	27.9

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Desaturation Analysis - 8 Guinea Pigs

CONCENTRATION	A/A_0	$T_{1/2}$ (MINS)	No. ANIMALS
1	.419 - .71	1.5 - 2.5	7
2	.039 - .49	5.0 - 11.0	18
3	.41 - .63	21.5 - 43.7	5
4	.009 - .17	98.0 - 270.0	7

ACTIVITY LOSS	10%	50%	90%	95%
TIME (MIN.)	1.77	13.3	37.1	132
σ	.27	3.45	11.1	23.9

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^{85}Kr Partition Coefficients

Tissue	Part	Tissue:Blood	Tissue:Air
Brain	Cortex	0.92 (Hc=50)	
	White	1.26 (Hc=50)	
Kidney	Cortex	1.0	
		0.96	
	Medulla	1.0	
Fat		9	
			0.54
		5	
Liver		1.06	
		1.04	
Eye	Retina	1.0	
Skeletal muscle		1.0	
Testis		0.85	
Blood			0.05-0.06

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